Non-random autosome segregation

Schwander, Tanja; Beukeboom, Leo W.

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Non-random autosome segregation: A stepping stone for the evolution of sex chromosome complexes?

Sex-biased transmission of autosomes could facilitate the spread of antagonistic alleles, and generate sex-chromosome systems with multiple X or Y chromosomes.

*Tanja Schwander** *and Leo W. Beukeboom*

A new study in *Caenorhabditis elegans* shows that homologous autosomes segregate non-randomly with the sex chromosome in the heterogametic sex. Segregation occurs according to size, small autosomes segregating with, and large autosomes segregating away from the X-chromosome. Such sex-biased transmission of autosomes could facilitate the spread of sexually antagonistic alleles whose effects favor the fitness of one sex at the expense of the other. This may provide a first step toward the evolution of new sex determination systems.

Keywords:
- chromosome segregation; conflict; sex determination; sexual antagonism

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Evolutionary Genetics, Center for Ecological and Evolutionary Studies, University of Groningen, Groningen, The Netherlands

***Corresponding author:**
Tanja Schwander
E-mail: tanja.schwander@gmail.com

Introduction

During the development of the "Mendelian-chromosome theory of heredity" by Thomas Hunt Morgan and his fellow geneticists between 1905 and 1920, one of the fundamental challenges they faced was to demonstrate that chromosomes segregate randomly during meiosis. It was known that genes segregate randomly during meiosis and since genes are located on chromosomes, then it must follow that chromosomes also segregate randomly during meiosis. The cytological "proof" of this is generally credited to Estrella Eleanor Carothers. She analyzed the segregation of chromosomes during the first meiotic division in short-horned grasshoppers, where several autosomes occur as cytologically distinguishable "small" and "large" versions [1]. Short-horned grasshoppers have a XX:XO sex determination system; individuals with two X-chromosomes develop into females, whereas individuals with only one X develop into males. Thus, by using males which were heterozygous for a given size-variable autosome, Carothers could test for random chromosome segregation by counting how many times the small and large autosome of a pair segregate with the X or away from it. Among 300 analyzed spermatocyte cells, the small autosome segregated away from the X-chromosome in 154 cells and with the X-chromosome in the remaining 146 cells. This ratio corresponded well to the 50:50 split expected for random segregation ($p = 0.69$ in a binomial test).

It appears that Carothers was fortunate in choosing to study a species in which size differences between autosomes did not affect their segregation with the sex chromosome. A recent study in *Caenorhabditis elegans* [2] shows that even subtle size differences between homologous autosomes can result in segregation biases with the X-chromosome. In *C. elegans*, males have a single X-chromosome, but individuals with two sex-chromosomes are hermaphrodites. Wang et al. [2] crossed males which where heterozygous for different

integrated transgenes with wild-type hermaphrodites and analyzed the proportion of male and hermaphrodite offspring which inherited the large autosome (i.e. the one comprising the transgene) versus the small one. In the absence of sex-specific mortality effects generated by the transgenes, random chromosome segregation predicts that half of all males, and half of all hermaphrodites, should inherit the large autosome. However, this was not the pattern they observed. Instead, the large autosome preferentially segregated away from the X-chromosome, whereas the smaller autosome preferentially segregated together with the X-chromosome, resulting in a significantly higher proportion of males than hermaphrodites inheriting the large autosome (Fig. 1). Although a direct test for sex-specific mortality effects due to the transgenes (i.e. equal frequencies of the two autosomes in male and hermaphrodite offspring produced by a hermaphrodite heterozygous for the integrated transgenes mated to a wild-type male) was not conducted, the results observed in this study are unlikely to stem from sex-specific mortality effects. Indeed, the authors observed very little mortality overall, whereas almost 50% mortality would be required to account for the most extreme segregation bias. In addition, autosome size differences resulted in sex-biased segregation for each of the five autosome pairs independently of whether autosome size differences stemmed from the addition of transgenes or from the deletion of portions of autosomes. It is notable that non-random segregation occurred even for very small indels. Insertions of 33 kb and deletions of only 1.1 kb resulted in a slight sex-biased transmission of the autosomes. Larger size differences between autosomes generated greater segregation bias, with the largest insertion (~7.3 Mb) resulting in a greater than six-fold larger proportion of hermaphrodites than males inheriting the short autosome.

In Carother's grasshoppers, the size differences between autosomes must have been considerable, given that she was able to visually identify the small and large autosomes under a bright field microscope. Had these differences had similar effects on segregation relative to the X-chromosome as in *C. elegans*, the general acceptance of the "Mendelian-chromosome theory of heredity" may have been delayed for several years.

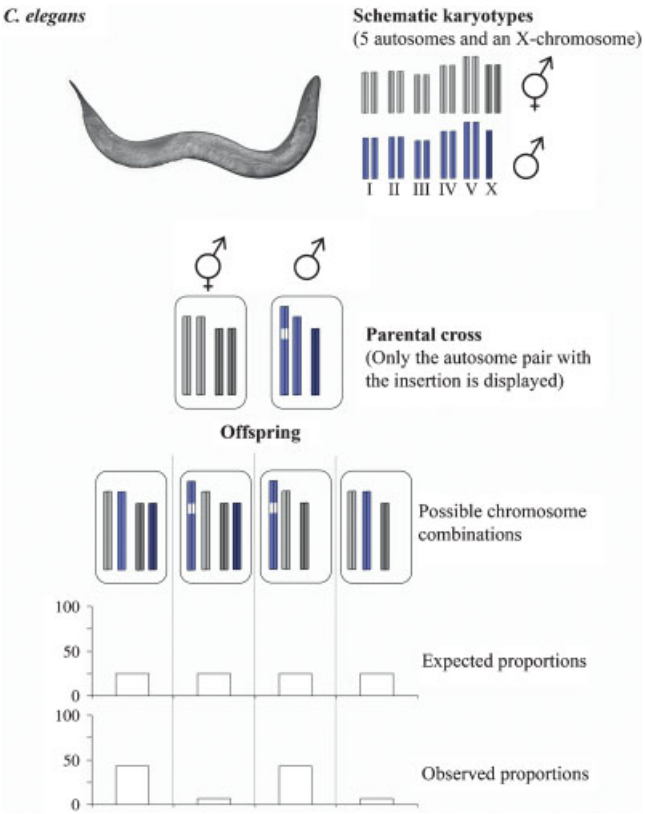

Figure 1. Non-random chromosome segregation in *C. elegans*. When males heterozygous for an integrated transgene (indicated by the white fraction in chromosome V) are mated to wild-type hermaphrodites, the autosome comprising the transgene preferentially segregates away from the X-chromosome, whereas the smaller autosome preferentially segregates together with the X-chromosome [2].

Non-random chromosome segregation could affect genome size evolution and favor the spread of sexually antagonistic alleles

A sex-biased transmission of certain autosome variants can have at least two important consequences. First, as pointed out by Wang et al. [2], it can result in a reduction of genome size in a male:hermaphrodite species such as *C. elegans* if males are occasionally lost from the population. This is because the majority of the large autosomes will occur in males so that the elimination of males from the population will directly decrease the proportion of large autosomes. Self-reproducing hermaphrodites produce occasional males as a consequence of non-disjunction of the X-chromosomes. Accordingly, the loss of males in one generation does not result in a transition to a hermaphrodite-only lineage without males. Consistent with the predicted effect of segregation bias on genome size evolution, Wang et al. [2] found that male:hermaphrodite species indeed have smaller genomes than male:female species in the genus *Caenorhabditis*.

Second, sex-biased segregation of certain autosomes could facilitate the spread of sexually antagonistic alleles whose effect favors the fitness of one sex at the expense of the other [3, 4]. The reproductive interests of males and females often do not coincide, which results in divergent selective pressures acting on each sex (for an example see [5]). This may generate an evolutionary arms race between the sexes for control of reproduction, mediated by the evolution of sexually antagonistic genes [6]. This presents a problem for a single locus with different male and female fitness optima. Since net selection depends on fitness effects in both sexes, it is difficult for a sexually antagonistic allele to invade a population if it occurs equally as often in males and females, which is usually the case for genes located on randomly segregating autosomes.

In contrast, a sexually antagonistic allele is expected to spread more easily if located on a chromosome with a sex-biased transmission pattern. This has been shown theoretically for sex-chromosomes [6] and empirical evidence in

Drosophila indeed suggests an excess of sexually antagonistic genes on the sex chromosomes as compared to the autosomes [7–9]. Importantly, the same principle should also hold for less extreme sex-linked transmission, such as for the small versus large versions of the different autosomes in *C. elegans*. In such a system, sexually antagonistic alleles should be more likely to spread if they are linked to long stretches of DNA, because the presence versus absence of a linkage group would generate size differences between autosomes and thereby a sex-biased transmission pattern. Subsequently, recruitment of additional antagonistic alleles into an extant linkage group may occur. Thus, if autosomes in natural *C. elegans* populations vary in size, which is likely to be the case [10], it is predicted that the larger versions of a given autosome (most frequently found in males) will comprise an excess of alleles which are advantageous for males but disadvantageous for hermaphrodites. Conversely, the small versions of a given autosome will comprise an excess of alleles which are disadvantageous for males but advantageous for hermaphrodites.

Non-random chromosome segregation as a first step toward the evolution of new sex determination systems?

The presence of sexually antagonistic alleles on an autosome could result in selection for mechanisms generating even stronger co-segregation of certain autosome versions with the X-chromosome, thereby blurring the distinction in inheritance between sex-chromosomes and autosomes. A perfect co-segregation of a size-variable autosome with the X-chromosome has been documented in another insect species with XX:XO sex determination, the mole cricket (*Gryllotalpa*). During meiosis in mole cricket males, the large autosome in a specific pair always segregates together with the X-chromosome, whereas the small variant always segregates away from it (i.e. the opposite of the pattern documented for *C. elegans*) [11–14]. Although it is not known whether the size-variable autosome carries any essential function for male and female fitness in the mole cricket, recruitment of such genes is expected to occur for chromosomes with sex-linked transmission [15]. Thus, starting with a small size-dependent segregation bias, increasingly strong co-segregation of an autosome with the extant sex chromosome may give rise to new complex sex determination systems involving multiple different X and Y chromosomes. Systems where multiple X or multiple Y chromosomes co-segregate in chains have been documented in a variety of species, including spiny anteaters (Echnida) and the platypus [16, 17], as well as other vertebrates and many invertebrates [13]. However, the evolution of these systems has thus far been difficult to explain [18, 19]. Testing for non-random autosome segregation in these species may provide new insights into the origin of such systems.

Conclusions

The study by Wang et al. [2] has shown that subtle, non-adaptive size differences between homologous autosomes can result in sex-biased segregation patterns. It remains to be investigated whether autosome variants with sex-biased transmission in natural populations harbor, as we predict, an excess of sexually antagonistic alleles and if antagonistic alleles located on autosomes tend to be in large linkage groups.

Another question remaining to be answered is what is the mechanism underlying the segregation bias in *C. elegans* and the mole cricket, and whether similar or different mechanisms generate segregation biases in different species. While there is currently no information available on the proximate causes of the segregation bias, many different cytological mechanisms have the potential to generate non-random chromosome segregation by affecting chromosome arrangement and migration. For example, certain chromosomes may tend to lag behind during meiosis as a consequence of different heterochromatin and telomere structures [20], and these may find themselves together in the same daughter cell. Other chromosome properties, such as whether they comprise a clearly defined centromere, or are ''holocentric'', with the entire chromosome acting as the centromere, such as in *C. elegans*, could also be important because large holocentric chromosomes have more anchor points for the spindle than small ones. Therefore, a significant next step will be to identify the mechanisms resulting in non-random segregation of differently sized autosomes in *C. elegans* and the mole crickets, and to explain the apparent lack thereof in Carother's short-horned grasshoppers. Given the potentially broad consequences of the sex-biased segregation of autosomes, tests on how autosome size influences their segregation with the sex chromosomes in other species would be highly warranted.

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